TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
D 2145 PCT/2		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/08827	08/09/2000	10/09/1999
Applicant		
EPIDAUROS BIOTECHNOLOGIE AG et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 10 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readble form.

   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ because the applicant failed to suggest a figure.

   ☐ because this figure better characterizes the invention.

   ☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/08827

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,33,34,37
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-43 all partially

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,33,34,37

Present claims 1 and 37 relate to an extremely large number of polynucelotide sequence of which only a small fraction could be unambiguously allocated to the hPXR variants. In fact, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those sequences succesfully allocated with the help of tables 1,3 and 4.

Claims 33 and 34 refer to an inhibitor identified or obtainable by screening compounds which in contact with an hPXR variant would be capable of providing a detectable signal in response to drug metabolization. No such compounds are defined in the application. In consequence the scope of said claim is ambigous and vague, and its subject-matter is not sufficiently disclosed and supported (Art. 83 and 84 EPC). Therefore, no search can be carried out for such speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M20 (having a nucleotide substitution at position -201), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

2. Claims: 1-43 all aprtially

A molecular variant of the hPXR, the so-called M1 (having a nucleotide substitution at position -131), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

3. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M21 (having a nucleotide substitution at position -57), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

4. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M6 (having a nucleotide substitution at position -42), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

5. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M5 (having a nucleotide substitution at position 52), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors

capable of modulating the activity of a molecular variant of hPXR.

6. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M7 (having a nucleotide substitution at position 79), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

7. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M4 (having a nucleotide substitution at position 106), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

8. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M8 (having a nucleotide substitution at position 225), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

9. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M23 (having a nucleotide substitution at position 315), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

10. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M10 (having a nucleotide substitution at position 418), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors

capable of modulating the activity of a molecular variant of hPXR.

11. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M11 (having a nucleotide substitution at position 488), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

12. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M12 (having a nucleotide substitution at position 492), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

13. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M13 (having a nucleotide substitution at position 543), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

14. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M14 (having a nucleotide substitution at position 696), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

15. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M24 (having a nucleotide substitution at position 834), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors

capable of modulating the activity of a molecular variant of hPXR.

16. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M25 (having a nucleotide substitution at position 984), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

17. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M27 (having a nucleotide substitution at position 1108), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

18. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M19 (having a nucleotide substitution at position 1308), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

19. Claims: 1-43 all partially

A molecular variant of the hPXR, the so-called M28 (having a nucleotide substitution at position 1320), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleutides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of hPXR.

INTERNATIONAL SEARCH REPORT

International Application No
EP 00/08827

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68 C12P19/34 C12N9/02 C07K16/18 C12N15/53
A61K38/17 A61P35/00 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOTZLAW H ET AL.,: "The human organ receptor PXR messenger RNA is expressed in both normal and neoplastic breast tissue." CLINICAL CANCER RESEARCH, vol. 5, August 1999 (1999-08), pages 2103-2107, XP000929536 the whole document ---	1-43
X	LEHMANN J M ET AL.,: "The human orphan nuclear receptor PXR is activated by compounds that regulate CYP3A4 gene expression and cause drug interactions." JOURNAL OF CLINICAL INVESTIGATION, vol. 102, 1 September 1998 (1998-09-01), page 1016-1023 XP000909297 cited in the application the whole document --- -/--	1-3,12, 35-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	05.06.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BERTILSSON G. ET AL.,: "Identification of a human nuclear receptor defines a new signaling pathway for CYP3A induction" PROC. NATL. ACAD. SCI. U.S.A., vol. 95(21), 1998, page 12208-12213 XP002921167 cited in the application the whole document	1-3,12, 35-37
X	KLIEWER S A ET AL: "AN ORPHAN NUCLEAR RECEPTOR ACTIVATED BY PREGNANES DEFINES A NOVEL STEROID SIGNALING PATHWAY" CELL,CELL PRESS, CAMBRIDGE, NA,US, vol. 92, 9 January 1998 (1998-01-09), pages 73-82, XP000918927 ISSN: 0092-8674 the whole document	1-3,12, 35-37
A	PASCUSSI J-M ET AL.,: "Evidence for the presence of a functional Pregnane X Receptor response element in the CYP3A7 promoter gene." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 260, 5 July 1999 (1999-07-05), page 377-381 XP000907111 cited in the application the whole document	1-3,12, 20
A	ZHANG HE ET AL: "Rat pregnane X receptor: Molecular cloning, tissue distribution, and xenobiotic regulation." ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 368, no. 1, 1 August 1999 (1999-08-01), pages 14-22, XP000933837 ISSN: 0003-9861 the whole document	1-3,12, 20
P,X	WO 99 48915 A (GLAXO GROUP LTD ;KLIEWER STEVEN ANTHONY (US); WILLSON TIMOTHY MARK) 30 September 1999 (1999-09-30) the whole document	1-43
P,X	JONES STACEY A ET AL: "The pregnane X receptor: A promiscuous xenobiotic receptor that has diverged during evolution." MOLECULAR ENDOCRINOLOGY, vol. 14, no. 1, January 2000 (2000-01), pages 27-39, XP000933600 ISSN: 0888-8809 the whole document	1-43

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INTERNATIONAL SEARCH REPORT

International Application No
[redacted]/EP 00/08827

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 1 024 193 A (CHUGAI PHARMACEUTICAL CO LTD) 2 August 2000 (2000-08-02) the whole document	1-43

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
/EP 00/08827

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9948915 A	30-09-1999	AU 3211699 A	18-10-1999
		EP 1066320 A	10-01-2001
EP 1024193 A	02-08-2000	AU 8356498 A	16-02-1999
		WO 9905292 A	04-02-1999
		JP 11127871 A	18-05-1999